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A study of serum testosterone as a prognostic indicator in patients with respiratory failure on mechanical ventilation

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Abstract---Patients on mechanical ventilation tend to have a multitude of biochemical changes, many due to adrenal suppression or functional adrenal insufficiency. Abnormal levels of gonadal steroids poses significant physiologic effects in critically ill patients. Hypotestosteronemia, defined as a serum total testosterone level <250 ng/dL (<8.7 nmol/L) or free testosterone level <0.75 ng/dL (<0.03 nmol/L), is a common finding among male patients with critical illness. In this study we determine if serum testosterone can be used as a prognostic indicator in patients with respiratory failure, on mechanical ventilation. This is a prospective observational study done over a period of 18 months at a tertiary care center in Mysore. Study participants included male patients admitted to ICU of JSS Hospital with documented acute respiratory failure on arterial blood gas analysis (ABG), who were mechanically ventilated for more than 24 hours. Blood sample was collected at 24 hours and 72 hours post intubation and serum testosterone levels were estimated using Electro Chemiluminescence assay. Our results indicate 90.5% of the patients had low testosterone levels at 24 hours, whereas 97.1% of the patients

had hypotestosteronemia at 72 hours post intubation. There is a significant decline (P-value-0.301) in serum testosterone levels at 72 hours post intubation. Hence, there seems to be a higher prevalence of hypotestosteronemia with prolonged duration of mechanical ventilation. However, the severity of hypotestosteronemia did not correlate significantly with prolonged ICU stay. It has been observed that all the patients who succumbed to the illness had sub-optimal levels of serum testosterone. Additionally, there is a significant correlation (P-value-0.045) between the severity of hypotestosteronemia and survival status of the patient. The mortality rate was 48.1%, 7.4% and 44.4% among patients with serum testosterone levels of <50ng/ml, 51-100ng/ml and 100-241 ng/ml, respectively. The significant prevalence of hypotestosteronemia and the associated mortality in male patients on mechanical ventilation suggest the screening for serum testosterone levels as a prognostic indicator.

Keywords---endocrine, critical illness, testosterone, respiratory failure, mechanical ventilation.

Introduction

Hypotestosteronemia, which is defined as a serum total testosterone level <250 ng/dL (<8.7 nmol/L) or free testosterone level <0.75 ng/dL (<0.03 nmol/L) ⁽⁹⁾, is a common finding among male patients with critical illness^(6,7,10) It is due to various factors which include, impaired regulation of the hypothalamo-pituitary-gonadal axis, increased peripheral aromatization of androgens and direct effects that the cytokines have on Leydig cell function ^(2,5,11). Studies have been undertaken to correlate the levels of serum testosterone in sepsis, trauma, etc. But there are a very few studies that aim to find a correlation of serum testosterone levels in patients with respiratory failure, on mechanical ventilation and its value in prognostication.

Several studies have reported abnormal levels of gonadal steroids posing significant physiologic effects in critically ill patients. These effects include suppression of adrenal function, pituitary responses, and the reproductive axis. Patients on mechanical ventilation tend to have a multitude of such changes, many due to adrenal suppression or functional adrenal insufficiency. A study by Almoosa et al observed association of low testosterone levels with respiratory failure ⁽¹⁵⁾. Another study evaluating serum testosterone levels in men with primary respiratory failure, including COPD (Chronic obstructive pulmonary disease) patients, indicated a significant correlation between the degree of arterial hypoxia and the severity of testosterone suppression ⁽¹⁶⁾. An India centric study in this regard is lacking. In this study we assessed the prevalence of hypotestosteronemia and its severity in Indian male patients with respiratory failure, who are on mechanical ventilator support. The study also aims to establish the relationship between serum testosterone levels, the severity of hypotestosteronemia and its outcomes.

Material and Methods

A single centre prospective study of 105 patients, conducted at JSS Hospital, Mysore, India for a duration of 18 months from 2017-2019. The material for study was formed by adult patients admitted to ICU in JSS Hospital. Duration: 18 months that is from 2017-2019. Informed patient consent and institutional ethics committee approval were obtained for the conduct of the study. Any registration number (---). Study population: ICU patients, all male >18 years of age, with documented respiratory failure on ABG who are on mechanical ventilation for >24 hours.

Patients with chronic liver disease or Hypotestosteronemia due to other causes such as hypogonadism, testicular atrophy, were excluded from the study. The normal testosterone reading falls between 300 to 1000ng/dL. Hypotestosteronemia in patients is defined as a serum total testosterone level <250 ng/dL (<8.7 nmol/L). Data collection and analysis: Blood sample was collected 24 hours post intubation and 72 hours post intubation. Serum testosterone was estimated in the above-mentioned subjects by Electro Chemiluminescence assay using Elecsys testosterone-II kit according to manufacturer's instructions. Statistical Analysis was performed using SPSS software. Difference in proportions was calculated using chi-square test. Statistical significance was considered at 5% level of significance.

Results

Table 1: Baseline characteristics

	Number of subjects	Percentage (%)
Total	105	
Age (years)		
18-30	16	15.2
31-50	37	35.2
51-70	44	41.9
70+	8	7.6
Total leukocyte count (Cells/mm ³)		
<11 k	54	51.4
11-20 k	45	42.9
>20 k	6	5.7

Table 2: Serum testosterone values at 24 and 72 hours post intubation

Serum testosterone (ng/ml)		Duration post intubation (Total N=105)	
		24 hours	72 hours
<241	N	95	102
	%	90.5%	97.1%
	Mean		
241-827	N	10	3

	%	9.5%	2.9%
	Mean		

Among the included study population, about 92% were adults (18 to 70 years) and 8% were elderly (>70 years) patients (Table 1). The serum testosterone levels were suboptimal (<241 ng/ml) in majority (94%) of the patients. Comparing the outcomes following an intubation period of 24 h and 72 h, there is a significant increase ($P=0.045$) in the prevalence of hypotestosteronemia at 72 hours post intubation. Additionally, with prolonged intubation period, the mean levels of serum testosterone decreased drastically from a mean value of 155 ng/ml at 24-h to 100 ng/ml at 72 h post- intubation (36 % mean reduction).

Table 3: Survival status and association of hypotestosteronemia

Survival status	Total population (N=105)	Prevalence of hypotestosteronemia				
		Yes (<241 ng/ml)				No >241 (ng/ml)
		Total	(<50 ng/ml)	51-100 (ng/ml)	>100-241 ng/ml	
Alive	78	75 (96.2%)	18 (24%)	11 (14.7%)	46 (61.3%)	3 (3.8%)
Dead	27	27 (100%)	13 (48.1%)	2 (7.4%)	12 (44.4%)	0

All the individuals (100%) who did not survive had hypotestosteronemia (<241 ng/ml). Patients who died had an average suboptimal serum testosterone level of 125.36 ng/ml. Among those critically ill patients who survived, 96% had low serum testosterone levels. The extent of severity of hypotestosteronemia indicates that about 50% of the dead population had <50 mg/ml of serum testosterone levels.

Table 4: Comparison between severity of hypotestosteronemia at 72 hours post intubation and duration of ICU stay

Serum testosterone at 72 hours (ng/ml)	Mean duration of ICU stay (no. of days)
<50	6
51-100	5.53
>100	6.4

Mean duration of ICU stay was around 6 days in patients who had low serum testosterone levels. However, there was no significant correlation between duration of ICU stay and severity of hypotestosteronemia in our study population.

Discussion

Hypotestosteronemia is one of the common biochemical abnormalities encountered in chronic critical illnesses. Many theories have been proposed for the same, but the most accepted one is a possible adrenal deficiency or a functional adrenal insufficiency in critical illness⁽⁵⁴⁾. In our study, we included male patients with respiratory failure, who were on mechanical ventilation and aged over 18 years with no history of chronic liver disease. Serum testosterone was estimated at 24 hours post intubation and 72 hours post intubation and results were analysed and correlated with duration of ICU stay and survival status of the patient.

The results from our study indicated that hypotestosteronemia is a common biochemical finding in patients with respiratory failure who were on mechanical ventilation. 97% of the critically ill patients had hypotestosteronemia following 72 hours intubation period (P-value of 0.045). Serum testosterone levels continued to significantly decline with increase in intubation period. This similar finding of hypotestosteronemia in critical illness has been observed in many other studies⁽⁶⁻¹⁰⁾. Low serum testosterone levels may have an impact on clinical outcomes, affecting muscular performance which further results in requirement of prolonged intubation times and mechanical breathing. Many other illnesses, such as myocardial infarction, sepsis, or surgery, cause a rapid and significant drop in serum testosterone levels. A rise in serum cortisol that occurs with critical illnesses could be one cause. On follow-up, there was a drop in lean mass or a reduction in exercise tolerance. This sample was chosen for our study because low testosterone levels may contribute to poorer respiratory muscles, and there may be a link between the length of time spent in the ICU and hypotestosteronemia. Long-term mechanical ventilation has been linked to diaphragm and respiratory muscle mass weakness, according to certain publications. Hypotestosteronemia, while thought to be one of the causes, has yet to be verified in a study, necessitating the need for more research to discover if low testosterone levels are the source of these abnormalities.

Of the 27 deaths among the 105 people who took part in our study, all of them had hypotestosteronemia (below than 240 ng/ml) (Table 4). Almost 50% of the dead population had <50 mg/ml of serum testosterone levels. Even among the survivors, the prevalence of hypotestosteronemia is 97%. Considering the significant prevalence of low serum testosterone levels among critically ill patients, correlation of declining levels in patients requiring prolonged intubation and all the dead patients with hypotestosteronemia condition, serum testosterone levels could be a strong prognostic indicator in critically ill patients requiring mechanical ventilation.

Limitations

1. This study focused entirely on male population. However, alterations in androgen levels can occur in female patients with a critical illness and this may affect their outcome too.

2. We did not measure other factors that contributed to or resulted from low serum testosterone levels, like muscle weakness or effects of metabolism. Without these, we could not measure effects of specific outcomes.
3. Few of our patients had acute kidney injury, sepsis and this could have added to the severity of hypotestosteronemia.
4. Serum testosterone may be physiologically low in elderly (>70 years) who constituted 7.6% of our study population.

Future Directions

Future prospective studies comparing the prevalence of hypotestosteronemia in other patients and interventional studies that study the effect of supplementation of testosterone on prognosis and outcome will be useful.

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